Nanocrystalline Hydroxyapatite-Based Material Already Contributes to Implant Stability After 3 Months: A Clinical and Radiologic 3-Year Follow-up Investigation

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The present study reports on a 3-year clinical and radiologic follow-up investigation of dental implants placed 3 and 6 months after sinus augmentation in 14 patients. Augmentation was performed with a synthetic bone substitute material composed of nanocrystalline hydroxyapatite. The aim of the study was to determine how the integration period of the bone substitute material, that is, 3 months or 6 months, influences implant integration within the patient's upper jaw. Therefore, the following clinical and radiologic parameters were investigated: implant being in situ; Periotest value; and presence of peri-implant osteolysis, bleeding on probing, plaque, and soft tissue recession around the implants. At the follow-up investigation 3 years after placement, 23 of 24 implants were in situ and suitable for prosthetic rehabilitation. No implants in either study group were mobile or showed peri-implant osteolysis. Only a few implants showed plaque or soft tissue variations. Within its limits, the present study showed comparable clinical performance of dental implants placed 3 months after sinus floor augmentation to implants placed 6 months after augmentation. The results of all investigated parameters were in accordance with results found in the literature. It can be concluded that augmentation with the applied synthetic bone substitute material already forms a sufficient implantation bed 3 months after augmentation, which enables long-term, stable, implant-retained restoration. These findings might contribute to a reduced healing time after augmentation, which would be favorable for patients and clinicians.

Key Words: NanoBone, hydroxyapatite, sinus floor augmentation, bone substitutes, dental implants

INTRODUCTION

Due to alveolar atrophy or extremely pneumatized maxillary sinus, alveolar height can be reduced to a few millimeters, and thus, augmentation is needed before dental implants are inserted. Sinus floor elevation with augmentation of the subantral space is a well-documented and reliable intervention to enlarge the maxillary bone volume. Since its initial introduction by Tatum[1] and Boyne and James,[2] various techniques have been developed and different materials for augmentation have been investigated. Autologous bone, with its osteoinductive, osteogenic, and osteoconductive potential, is postulated to be the gold standard in bone augmentation.[3] Osteogenic cells transferred within the bone transplant are able to recruit mesenchymal stem cells from the surrounding tissue to differentiate into osteoblasts. However,

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the need for a second stage, the risk of donor-site morbidity, the limited availability, and sometimes the need for general anesthesia are inherent drawbacks and increase the demand for bone substitute materials.[4]

Allografts of human origin or xenografts from coral, bovine, or equine demineralized bone matrix avoid the risks related to a second operation. However, the extensive processing techniques (eg, lyophilization or freeze-drying) that are necessary to eliminate their potential immunogenic properties[5] reduce the biological abilities compared with autogenous grafts.[6] In the past years, a large number of synthetic bone substitutes, including hydroxyapatite (HA), biphasic calcium phosphate ceramics, and α- and β-tricalcium phosphate, have been developed. Most of these fillers basically serve as scaffolds for the ingrowth of new bone.[7]

The choice of a graft material has to be made with regard to the given constitution of the defect, that is, type, size, and localization, as well as the type of intervention and material characteristics. Regarding the integration time of the augmented material, no clear consensus is found in the literature. Depending on the amount of residual bone and therefore the ability to insert implants with a high torque and primary stability, 1-stage and 2-stage surgical procedures have been reported. In the case of a residual alveolar height <3 mm, a 2-stage surgical protocol with an integration time of 6 months for the biomaterial seems to be preferred.[8–10]

Recently, the research work group investigated a silica-based nanocrystalline HA bone substitute material, NanoBone (NB, Artoss, Bremen, Germany), in a consecutive number of animal studies and clinical trials. In an in vivo trial in Wistar rats, tissue reaction, vascularization, and tartrate-resistant acid phosphatase (TRAP) positive and TRAP-negative multinucleated giant cell reaction to implantation of NB in subcutaneous tissue was analyzed for 6 months. The results showed an almost complete material degradation without a severe inflammatory response.[11]

A second in vivo trial in caprine muscle tissue revealed cellular degradation of the biomaterial by the same TRAP- positive and TRAP-negative multinucleated giant cells. Also, after an observation period of 6 months, only few granules of the HA-based biomaterial were detected without any signs of new bone formation within the implantation bed.[12]

After the in vivo trials, the suitability of NB for sinus augmentation in humans was evaluated in a preliminary clinical trial of 20 human patients. Six months after implantation of the biomaterial, histologic analysis of extracted bone biopsies showed good integration of the biomaterial within the sinus cavity, high osteoclast activity at the margin of the biomaterial, and new trabecular bone formation directly adjacent to the biomaterial granules.[13]

In a split-mouth trial, the material-specific cellular tissue response of patients with head and neck cancer to the bone substitute NB and the bovine bone matrix Bio-Oss (Geistlich, Wolhusen, Suisse) was compared 6 months after implantation into the sinus cavity. Histologic analysis showed a higher vascularization and significantly higher induction of TRAP-positive multinucleated giant cells in the NB group than the Bio-Oss group. In both groups a comparable, satisfying extent of new bone formation and clinical performance of the dental implants was observed after 2 years of loading.[14]

After these promising results, a clinical trial was performed, in which NB was implanted in human sinus cavities and investigated histologically and histomorphometrically at 2 different time points of integration.[15] The biomaterial was augmented in 14 maxillary sinus cavities in 14 human patients with reduced denture and resorbed maxillary bone volume. Three and 6 months after augmentation ($n = 7$ patients implanted after 3 months; $n = 7$ patients implanted after 6 months) bone biopsies were extracted at the same time dental implants were inserted to analyze the tissue reaction and formation of new bone. Histologic and histomorphometric analysis revealed new bone formation in both groups, originating from the bone-biomaterial interface toward the central and cranial parts of the biopsies. No significant differences in the amount of newly formed bone were detected between the 3-month and 6-month groups ($24.89\% \pm 10.22\%$ versus $31.29\% \pm 2.29\%$). These results indicate that augmentation with this biomaterial might form a sufficient implantation bed even after an integration period of 3 month.

The aim of the present clinical study was to determine the influence of the integration period of

the bone substitute material, that is, 3 or 6 months, on implant integration within the patient's upper jaw.

Materials and Methods

Study design

From November 2007 till December 2009, 14 patients from the Department for Oral, Cranio-Maxillofacial and Facial Plastic Surgery, Goethe University Frankfurt, Germany received sinus floor augmentation and subsequent implantation. Study participants were 7 women and 7 men with an average age of 53.2 years (range = 34–77 years), reduced dentition in the molar region of the upper jaw, and severe resorbed maxillary bone. The study was approved by the Ethics Commission of the University of Frankfurt am Main and was carried out in accordance with the fifth revision of the World Medical Association Declaration of 2000. Patients were informed about the surgical procedure, the investigated biomaterial, and the study protocol and gave informed consent.

After sinus augmentation with the bone substitute NB, the participants were randomly divided in 2 groups. In the 3-month group, dental implants (Camlog ScrewLine, Camlog Biotechnologies, Basel, Switzerland) were inserted after a 3-month integration, and in the 6-month group implants were placed 6 months after augmentation. During the implantation process, one bone biopsy of the augmented region was extracted from each patient. Thus, 14 biopsies were gained histologic and histomorphometric analysis, as previously described.[15] Three years after implantation, 12 of 14 patients were willing to participate in the clinical 3-year follow-up investigation (Table 1).

Bone substitute material

The bone substitute material NB is completely synthetic composed from nanocrystalline HA with a mean particle size of 60 nm, embedded in a silica gel matrix with a pore size of 5–50 nm. During manufacturing with a sol-gel process and temperatures $<700^{\circ}C$, sintering of the HA can be avoided. The bone substitute material NB is characterized by numerous open links within the silica gel, which interact with the HA granules; an internal surface of 84 m^2/g; and a material porosity of 60%–80%.[16,17]

Table 1

Investigation parameters for clinical and radiologic 3-year follow-up investigation of dental implants placed in augmented maxilla

1. Implant being in situ
2. Periotest value
3. Presence of peri-implant osteolysis
4. Presence of bleeding on probing
5. Presence of plaque
6. Presence of soft tissue recessions around the implants

Clinical and radiologic follow-up investigation

Three years after placement, implants were investigated clinically and radiologically at the Department of Oral, Cranio-Maxillofacial and Facial Plastic Surgery, Goethe University Frankfurt, Germany, by the authors (S.G., J.L., and K.O.). The following parameters were investigated: implant survival, that is, implants being in situ; Periotest value (Medizintechnik Gulden, Modautal, Germany); presence of peri-implant osteolysis; bleeding on probing (BOP); presence of plaque; and presence of gingival recessions around the implants, which leads to exposition of the implant shoulder, abutment, or implant windings. Presence of peri-implant osteolysis was analyzed by radiologic images. The aforementioned parameters (mentioned in Table 1) were assessed in order to investigate the influence of the integration time of the augmented biomaterial on the clinical performance of the inserted implants.

Results

According to the study protocol, 3 and 6 months after sinus augmentation, 33 implants were inserted in 14 patients. Of these, 12 patients with 30 implants participated in the 3-year follow-up investigation. Of the 30 implants, 24 were placed in the augmented region of the upper jaw and 6 in the nonaugmented residual bone of the upper and lower jaw. The aim of this study is to determine how integration time of the augmented bone substitute material influences implant success. The follow-up investigation focuses on implants placed in the augmented upper jaw.

The 24 implants were divided in the 2 test groups as follows: 17 implants were placed 3 months after augmentation; 7 implants were placed after 6 months (Table 2).

TABLE 2

Patient age, distribution to study groups, number and site of inserted implants in the augmented and other sites, and type of prosthetic restoration

Patient	Age (y)	Study Group	Implants in the Augmentation Site	Implants in Other Sites	Prosthetic Restoration
1	65	3 month	14	-	Fixed
2	34	6 month	14	-	Fixed
3	56	3 month	5, 13, 14	-	Fixed
4	69	3-month	15	-	Fixed
5	No follow-up investigation				
6	61	3 month	3, 4, 5	-	Fixed
7	No follow up investigation				
8	35	6 month	14, 15	-	Fixed
9	72	3 month	2, 4, 5, 12, 13, 15	7, 9	Removable
10	57	3 month	13, 14	7, 8, 18, 30	Fixed
11	42	6 month	14, 15	-	Fixed
12	34	3 month	14	-	Fixed
13	36	6 month	4	-	Fixed
14	77	6 month	14	-	Fixed
Total			24	6	

Three years after insertion, 23 of 24 implants were in situ and suitable for prosthetic rehabilitation. One implant was lost in the 3-month test group 1 year after placement. This results in an implant survival rate of 95.8% for all placed implants and 94.1% for the 3-month test group. Eighteen implants was restored with fixed prosthetics, and 6 implants were supplied with removable dentures (Table 3).

The Periotest value of the 23 implants that were in situ at the follow-up investigation, varied between 0 and −8 (mean = −2.74). Between the 3- and the 6-month test group the average Periotest values varied slightly (3-month group = −2.94; 6-month group = −2.29) (Table 3).

Analysis of the recorded radiologic images showed no osseous peri-implant defects. In both

Table 3

Results of the 3-year clinical and radiologic follow-up investigation of implants inserted in the augmented region according to the investigation parameters (+ = positive/present, − = negative/absent)

Patient	Study Group	Implants in the Augmentation Site	Implant Loss	Perio-test Value	Peri-implant Osteolysis	Bleeding on Probing	Plaque	Recession
1	3 month	14	−	−8	−	+	+	−
2	6 month	14	−	−3	−	−	−	−
3	3 month	5, 13, 14	14	−3, −3, −	−	−	−	−
4	3 month	15	−	−1	−	−	+	−
5	No follow-up investigation							
6	3 month	3, 4, 5	−	−2, −8, −8	−	−, −, +	−, −, +	+, + ,+
7	No follow-up investigation							
8	6 month	14, 15	−	−1, −2	−	−	−	−
9	3 month	2, 4, 5, 12, 13, 15	−	−1, −3, −2, −2, −1, −1	−	−, −, +, −, −, +	−	−
10	3 month	13, 14	−	−1, 0	−	−	−	−
11	6 month	14, 15	−	−4, −3	−	+, +	+, +	−
12	3 month	14	−	−3	−	−	−	−
13	6 month	4	−	−2	−	−	−	−
14	6 month	14	−	−1	−	−	−	−
Total		24	1		−	6	5	3

groups, the peri-implant bone level of all implants reached the implant shoulder.

The BOP index was determined to describe the condition of the peri-implant soft tissue. The marginal gingiva was touched with a blunt periodontal probe to provoke bleeding as a sign of inflammatory reaction. In 6 of the 23 implants, bleeding was present, which corresponds to a BOP of 26.1%.

Accumulation of plaque at the gingival third of the implant suprastructure was obvious on 5 implants (21.7%). A distinct correlation between BOP and accumulation of plaque was found, as plaque was detected on 4 of 6 implants with BOP.

No notable difference regarding BOP and accumulation of plaque was observed between the test groups (3-month group: BOP = 4 implants, plaque = 3 implants; 6-month group: BOP = 2 implants, plaque = 2 implants) (Table 3).

Recession of the gingiva around the implants was observed on 3 implants (13.0%) of 1 patient with fixed prosthetic rehabilitation from the 3-month group. In the further clinical investigation these implants showed plaque accumulation and positive BOP (Table 3).

Figures 1 and 2 show radiographic images of patient 11 with 2 implants inserted in regions 14 und 15 immediately after placement and at the 3-year follow-up investigation. The peri-implant bone level reaches the implant shoulder at both images, and no signs of peri-implant osteolysis are obvious.

Figure 3 shows a clinical front image of patient 9 with implants in regions 2, 4, 5, 7, 9, 12, 13, and 15, restored with removable prosthetics at the 3-year follow-up investigation.

Figure 4 shows a close-up image of patient 9 with implants in regions 2, 4, and 5 and conical abutments for restoration with removable prosthetics. The peri-implant soft tissue is free from any signs of inflammation or recession.

Discussion

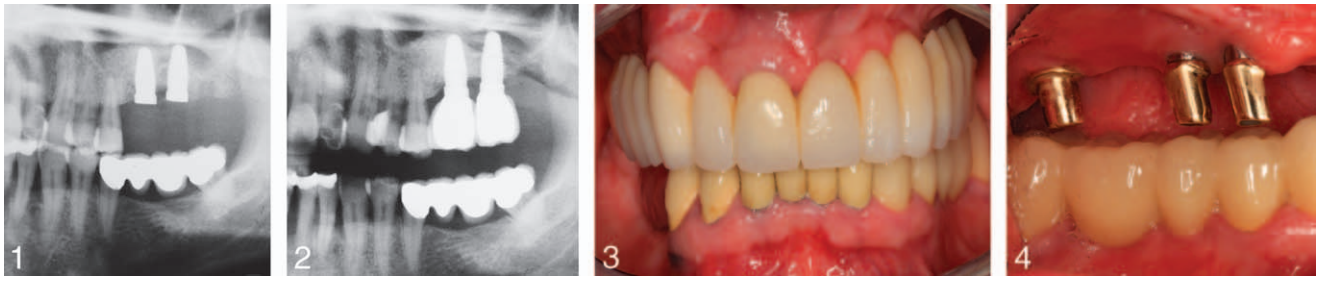
Sinus augmentation is one of the best documented and most promising augmentation techniques to enlarge the bone volume before implant placement.[8] With this technique, the local bone amount in the posterior maxillary region can be enlarged. A sufficient bony implantation bed is of striking importance as it guarantees safe osseointegration, which is needed for long-term implant stability.[18]

The aim of the present study was to analyze how a modification of the sinus augmentation protocol by reducing integration time to 3 months influences the clinical and radiologic performance of dental implants placed 3 months after augmentation. Therefore, implant survival, implant mobility, and peri-implant soft tissue conditions were assessed 3 years after implant placement. Altogether, 24 implants were placed, and of these, 23 implants were still present at the follow-up investigation, resulting in an overall survival rate of 95.8%. One implant was lost from the 3-month test group (survival rate of 94.1%); all implants from the 6-month group survived. No significant differences were detected between the 3- and 6-month groups. Both values were in accordance with survival rates of implants inserted in the posterior maxilla 6 months after augmentation. In a systematic review,[8] the survival rate of implants placed in the sinus 6 months after augmentation was 93.8%; the survival rate of simultaneously placed implants was 94.85%. Variations within the survival rates were found depending on the augmentation material and implant surface. The overall survival rate using 100% autogenous bone grafts was lower (88.9%) than the rates for combined grafts (94.7%) and 100% bone substitutes (96.1%), and textured surfaces achieved better outcomes than machined surfaces.[8]

Analysis of the Periotest values showed comparable results in both study groups: −2.94 in the 3-month group and −2.29 in the 6-month group. These results are in accordance with values achieved in comparable studies. In a clinical study, a mean Periotest value of −3.36 was reported in implants placed in the sinus 3 to 12 months after augmentation.[19]

It can be concluded then that implants placed 3 months after sinus augmentation have already achieved sufficiently high stability to guarantee safe osseointegration and support fixed or removable prosthetics.

In the radiologic analysis of orthopantogram records, no peri-implant osteolysis was detected in the 2 groups. Also, the bone level at all present implants was stable, and there were no vertical or horizontal incursions. These findings suggest that after 3 months a sufficient implantation bed has



Figures 1–4. Figures 1 and 2. Radiographic images of patient 11 with 2 implants inserted in regions 14 and 15 immediately after implant placement and at the 3-year clinical follow-up. The peri-implant bone level is stable and no peri-implant osteolysis can be detected. **Figure 3.** Clinical front image of patient 9 at the 3-year follow-up. Dental implants were inserted in regions 2, 4, 5, 7, 9, 12, 13, and 15 and restored with removable prosthetics. **Figure 4.** Close-up image of patient 9 with implants inserted in regions 2, 4, and 5 and conical abutments for restoration with removable prosthetics. The peri-implant soft tissue appears to be free of signs of inflammation or recessions.

already formed to enable complete osseointegration of the implants.

Assessment of BOP, plaque accumulation, and gingiva recessions on the implants was performed to assess implant contamination and consequently presence of a peri-implant infection. All of these parameters were more or less equal for implants from both study groups, and therefore, no higher prevalence of peri-implantitis was noted for the implants inserted earlier.

Numerous studies have investigated the formation of new bone in augmented regions 6 to 8 months after sinus augmentation with different bone substitute materials. The augmentation with a β-tricalcium phosphate based biomaterial revealed new bone formation of 20% 8 months after augmentation, whereas augmentation with a biphasic calcium phosphate achieved 27% new bone formation after 6 months.[20]

Sinus augmentation studies with a xenogenic demineralized bovine bone matrix showed 39.8% to 40% new bone formation after 6 months to 4 years and 46% after an observation period of up to 9 years.[21,22]

Results of a previous histologic and histomorphometric study revealed new bone formation of 24.89 ± 10.22% 90 days after augmentation with NB, which is comparable to new bone formation after 6 months (31.29 ± 2.29%) and to results in the literature.[20]

The 3-year clinical and radiologic follow-up analysis of the inserted implants confirmed the results of the histologic study, as no differences in survival and success of the implants were found. It seems that the extent of new formation after 3 months might be sufficient for a successful clinical implant. Furthermore, the results suggest that the new bone formation rate seems to be an indicator for subsequent implant survival and implant stability. The clinical data after 3 years of implant loading prove that the implants of both groups achieve comparable results for implant survival, implant stability, and peri-implant soft tissue conditions. However, to generally recommend implant placement 3 months after sinus augmentation with a synthetic bone substitute material, longer follow-up periods with this material; further prospective clinical, radiologic, and histologic studies with other synthetic-based materials' and larger patient population are necessary.

Conclusion

The present study analyzed the 3-year clinical and radiologic follow-up investigation of dental implants placed 3 and 6 month after sinus augmentation with a synthetic bone substitute material in 14 patients. Clinical and radiologic investigations showed comparable results for both groups for implant survival, implant stability, and peri-implant soft and hard tissue relations. Previously reported histologic and histomorphometric results showing a comparable amount of newly built bone 3 and 6 month after augmentation were verified by the similar clinical performance of the inserted dental implants.

The data from the present study are encouraging, as they show that the synthetic bone substitute

material already forms a sufficient implantation bed 3 months after augmentation and therefore accelerates the patient's oral rehabilitation.

Abbreviations

BOP: bleeding on probing
HA: hydroxyapatite
NB: NanoBone
TRAP: tartrate-resistant acid phosphatase

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